

REMARKS

Status of the Claims

Claims 14, 20-23 and 34-39 are currently pending in this application. Claims 23 and 34-36 were previously withdrawn as being directed to a nonelected invention. Claims 14, 20-22 and 37-39 were examiner and rejected. In this response, no claims are amended. Claims 14, 20-22 and 37-39 remain pending and subject to further examination.

Information Disclosure Statement

Applicants appreciate the Office's consideration of the documents submitted with the IDS filed on October 6, 2008.

Rejection under 35 U.S.C. § 103

Claims 14, 20-22 and 37-39 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,060,504 ("the '504 patent") in view of Cunningham *et al.* (*BMJ (British Medical Journal)* 2000, 321:778-779, hereinafter "Cunningham").

The Office stated that the '504 patent teaches N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide and its physiologically acceptable salt such as N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide hydrochloride (asimadoline) and the use of the compound for severe pain, hypersensitivity to pain, in particular inflammation-related hyperalgesias, and inflammation. The reference further allegedly teaches pharmaceutical preparations of the compound for oral, rectal, and parenteral administration and further discloses that the oral (i.e., systemic) administration is preferred.

The Office acknowledged that the '504 patent does not specifically teach the use of asimadoline for the treatment of post-herpetic neuralgia. To cure this deficiency of the '504 patent, the Office cited Cunningham, which allegedly teaches that post-herpetic neuralgia is a complication

after herpes zoster and is associated with scarring of the dorsal root ganglion and atrophy of the dorsal horn on the affected side (neuropathy), which follows the extensive inflammation and these and other abnormalities of the peripheral and central nervous system produce the pain and other unpleasant symptom of post-herpetic neuralgia, which include allodynia and hyperalgesia.

The Office asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use asimadoline taught by the '504 patent for the treatment of postherpetic neuralgia with a reasonable expectation of success because the '504 patent teaches that asimadoline is effective for the treatment of severe pain, hyperalgesias, and inflammation, which are typical symptoms of post-herpetic neuralgia as taught by Cunningham, and because Cunningham suggests that topical lidocaine and oxycodone, which are commonly used for severe pain, are effective for neuropathic pain and can be used for patients with herpes zoster. Accordingly, the Office argued that one of ordinary skill in the art at the time the invention was made would have been motivated to use asimadoline for the treatment of postherpetic neuralgia since asimadoline, which is effective for severe pain, hyperalgesias and inflammation, is expected to be useful for treating such symptoms of post-herpetic neuralgia.

Applicants respectfully traverse this rejection for the reasons set forth below.

The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, (Fed. Cir. 1993). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness a three-prong test must be met. First, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1731 (2007). Third, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Evidence of an unobvious or unexpected advantageous property can rebut *prima facie* obviousness. MPEP § 716.02(a) (emphasis added). “The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims... In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range.” *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) (emphasis added).

In this case, the claims are drawn to methods of treating neuropathy and related disorders by systemic administration of an effective dose of N-methyl-N-[(1 S)-1-phenyl-2-((3 S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide, and/or a pharmaceutically acceptable derivative, solvate, salt or stereoisomer thereof.

The ‘504 patent, which is owned by the assignee of the present application, teaches the use of N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide as a medicament for the treatment of inflammatory bowel disorders, neurodermatitis, pain and hypersensitivity to pain occurring in back complaints, burn injuries, sunburn and rheumatic disorders, inflammatory reactions occurring in this context, postoperative pain, hypersensitivity reactions to pain and the ileus frequently occurring after abdominal operations (col. 1, lines 43-63). The ‘504 patent further teaches that N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide and its physiologically acceptable salts antagonize inflammation-related hyperalgesias and are effective in the control of the actual inflammatory event (col. 2, lines 4-9). Additionally, the ‘504 patent teaches that N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide is effective against the pain associated with

rheumatic disorders and back conditions and positively affects the underlying inflammatory processes occurring in rheumatic disorders (col. 2, line 64 – col. 3, line 5).

Cunningham teaches that post-herpetic neuralgia is the most common complication of a herpes zoster infection that is associated with scarring of the dorsal root ganglion and atrophy of the dorsal horn on the affected side, which follows the extensive inflammation that occurs during herpes zoster (page 778). “These and other abnormalities of the peripheral and central nervous system produce the pain and other unpleasant symptoms of post-herpetic neuralgia, which include allodynia (pain occurring in response to normally innocuous stimuli), and hyperalgesia” (*id.*). Cunningham further teaches that “drugs such as topical lidocaine and oxycodone that have been shown to be efficacious in treating chronic neuropathic pain should be evaluated in patients with herpes zoster” (page 779).

The Office seems to assume that asimadoline’s known effectiveness against inflammation-related hyperalgesias is a predictor of its effectiveness against neuropathy-related hyperalgesias, which is entirely incorrect. The Office appears to conflate two distinct pathological states that have similar names but completely different underlying mechanisms. By way of background, Applicants respectfully refer the Examiner to companion review articles entitled “Mechanisms of inflammatory pain” (Kidd & Urban, *Br. J. Anaesth.* 2001, 87:3-11; enclosed as **Exhibit A**) and “Mechanisms of neuropathic pain” (Bridges *et al.*, *Br. J. Anaesth.* 2001, 87:12-26; enclosed as **Exhibit B**).

Kidd & Urban describe mechanisms of inflammatory pain and summarize the role of receptors, ion channels and neurotransmitters in the modulation of chemical, thermal and mechanical transduction. Kidd & Urban teach:

[P]ain arising from inflamed or injured tissues may arise spontaneously in the absence of an external trigger. Alternatively, responses to noxious stimuli may be enhanced (**hyperalgesia**) or normally innocuous stimuli may produce pain (**allodynia**). These features are not specific and do not, in themselves, allow recognition of distinct pathophysiological mechanisms. The movement-related symptoms of osteoarthritis and the touch-evoked pain of herpetic neuralgia are both examples of mechanical allodynia although they clearly arise from different mechanisms. Given limitations with the present terminology, the word

hyperalgesia will be adopted throughout this review to describe the state of pain hypersensitivity that accompanies inflammation.

(Kidd & Urban at page 3, emphasis added).

Kidd & Urban also teach that inflammation-induced hyperalgesia is mediated by receptors such as the vanilloid receptor VR-1, acid-sensing ion channels and P2X purinergic receptors (pages 5-6), voltage-gated ion channels such as the tetrodotoxin-resistant sodium channel SNS/PN3 and calcium channels (page 6), and inflammatory mediators such as, for example, bradykinin, tumor necrosis factor alpha (TNF α), interleukin 6 (IL-6), interleukin 8 (IL-8), prostaglandins, and neurotrophic growth factors (NGF) (pages 7-8). Kidd & Urban further teach that inflammation-induced hyperalgesia is usually treatable with non-steroidal anti-inflammatory drugs (NSAIDs) such as, for example, selective COX-2 inhibitors, opioid receptor agonists, and cannabinoid receptor agonists (pages 8-9).

In contrast, Bridges *et al.* teach that neuropathic pain originates in a damaged or abnormal nervous system and differs significantly from nociceptive or inflammatory pain:

Neuropathic pain is often reported as having a lancinating or continuous burning character and is often associated with the appearance of abnormal sensory signs, such as **allodynia** (pain as a result of a stimulus which does not normally provoke pain) or **hyperalgesia** (an increased response to a stimulus which is normally painful (Figure 1)... Neuropathic pain is an area of largely unmet therapeutic need. The current pharmacological mainstays of clinical management are tricyclic anti-depressants and certain anti-convulsants, but these only achieve clinically significant (greater than 50%) pain relief in less than 50% of patients and are associated with sub-optimal side effect profiles. Opioids are generally considered to be less effective in neuropathic pain than in inflammatory pain, with the dose response curve of opioids in neuropathic pain shifted to the right of that for inflammatory pain, although the extent of this difference is controversial.

(Bridges *et al.* at page 12, emphasis added).

Bridges *et al.* also teach that multiple mechanisms are responsible for the genesis of neuropathic pain, including peripheral mechanisms, such as ectopic and spontaneous discharge, ephaptic conduction, alterations in ion channel expression, collateral sprouting of primary afferent

neurons, sprouting of sympathetic neurons into the dorsal root ganglia (DRG), and nociceptor sensitization; and central mechanisms, such as central sensitization, spinal reorganization, cortical reorganization, and changes in inhibitory pathways (page 15).

With respect to the effect of opioids on neuropathic pain states, Bridges *et al.* further teach:

It is generally accepted that opioids are less effective in relieving neuropathic pain than inflammatory pain. Although the exact extent of this is controversial, the balance of evidence supports the view of an unfavourable (right) shift in the dose response function for opioids in neuropathy. There are a number of plausible explanations for this observation, including a loss of spinal opioid receptors and increased activity in physiological opioid antagonist systems (Fig. 6).

It is well established that a tertiary, peripheral site of opioid analgesia becomes operative during acute inflammation. Not only are the immune components of this phenomenon unlikely to be operating during painful neuropathy to the extent that they are during inflammation, but peripheral nerve injury is associated with Wallerian degeneration and, therefore, a loss of axonally expressed opioid receptors...

(Bridges *et al.* at page 21, emphasis added).

In summary, inflammation-induced hyperalgesia and allodynia have completely different underlying mechanisms from neuropathic hyperalgesia and allodynia. The former is caused primarily by transient changes in the concentrations of pro-inflammatory mediators and in the expression levels of certain receptors and ion channels that respond to those mediators. In contrast, the latter is caused primarily by permanent structural changes in the central and/or peripheral nervous system resulting from a variety of injuries. The effect of this distinction is profound. In the case of inflammatory pain, the pain and associated hyperalgesia and/or allodynia may be treated quite effectively by a broad range of anti-inflammatory agents. Once the inflammation is gone, so is the pain. In the case of neuropathic pain, however, the nervous system has undergone certain structural changes that are permanent in nature. For example, Cunningham teaches that scarring of the dorsal root ganglion and atrophy of the dorsal horn (i.e., permanent structural changes) follows the extensive inflammation that occurs during herpes zoster. Even though the nerve injury is caused by inflammation, post-herpetic neuralgia is not viewed as an inflammatory pain disorder because a

permanent nerve injury has taken place. These structural changes make treating neuropathic pain and related symptoms so much more difficult than treating inflammation-induced pain.

The fact that asimadoline is effective for treating inflammatory pain and inflammation-induced hyperalgesia was known well before the present invention was made. However, as Applicants have established above, inflammatory pain and hyperalgesia have very little, if anything, in common with neuropathic pain and hyperalgesia in terms of underlying pathophysiology. Consistent with this notion, most therapeutic agents that are prescribed for inflammatory pain (e.g., NSAIDs, opiates, etc.) are ineffective against neuropathic pain. A good analogy in this context would be common viral and bacterial infections. Although on the surface both types of infection produce similar symptoms (e.g., fever, sore throat, sneezing, runny nose), bacterial infections are susceptible to antibiotics, whereas viral infections are not. Thus, it would be highly unorthodox and nonobvious to use an antibiotic to treat a viral infection. Similarly, it was highly unorthodox and nonobvious to use asimadoline, a known inflammatory pain reliever, to treat neuropathic pain. For this reason, a person skilled in the art at the time the present invention was made would not have been motivated to combine the teachings of the '504 patent and Cunningham. Accordingly, it is respectfully submitted that a *prima facie* case of obviousness has not been established, and this rejection under 35 U.S.C. § 103(a) may properly be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **Docket No. 613242000900**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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